[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

THE ACTION OF THE GRIGNARD REAGENT ON α-OXIDO KETONES

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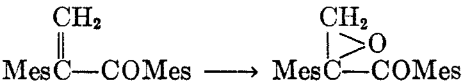
It has been shown by Grignard (1) and others (2) that ethylene oxides react less readily with Grignard reagents than do ketones. The attack of a Grignard reagent on α-oxido ketones was found by Kohler, Richtmyer, and Hester (3) to occur always at the carbonyl rather than the oxido group. An examination of this problem from a new viewpoint was made possible by the discovery that highly hindered α,β-unsaturated ketones readily formed epoxy derivatives. An example is the conversion of mesityl α-mesitylvinyl ketone (I) to the corresponding epoxide (II). This type of reaction has been effected with a number of ketones similar to I and has yielded a group of oxido ketones in which normal addition of Grignard reagents to the ketone group is not to be expected. These substances appeared, therefore, to provide an opportunity of determining the action of the Grignard reagent on the oxido group of such ketones without interference by the keto group.



$$\underset{\text{I}}{\mathrm{Mes}\overset{\overset{\displaystyle \mathrm{CH_2}}{\|}}{\mathrm{C}}\text{—COMes}} \longrightarrow \underset{\text{II}}{\mathrm{Mes}\overset{\overset{\displaystyle \mathrm{CH_2}}{|\!>\!\mathrm{O}}}{\mathrm{C}}\text{—COMes}}$$

Experiment has shown that the oxido group can, indeed, be transformed by the attack of a Grignard reagent and that the ketone group persists in the product. The change in the oxido group, however, proved to be most surprising. The oxygen atom was quantitatively removed and the product was the corresponding unsaturated ketone. Thus the oxide II, when treated with methylmagnesium iodide, reverted to the unsaturated ketone I. This amounts to the reduction of an oxide ketone to the corresponding unsaturated ketone, a type of reduction not previously associated with the Grignard reagent (4).

Although a satisfactory mechanism for this change has not been found, certain significant facts have been uncovered. By carrying out the reaction in the Grignard machine (5) it was shown that a mole of gas was evolved for every mole of oxido ketone which was used. The gas was proved by analysis to be methane.

Whatever the mechanism may be, it demands retention of a complex structure until the reaction mixture is decomposed. The unsaturated ketone must be formed at this point since it could not exist in the presence of the Grignard reagent; it has been shown to condense with this reagent (6).

It was found possible to extend the reaction to other closely related α-oxido ketones; namely, those from duryl α-mesitylvinyl ketone (III), isoduryl α-

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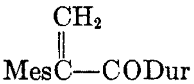
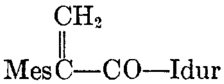
[1] DuPont Post-doctorate Research Fellow, 1940–1941.

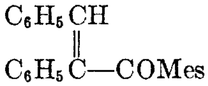
mesitylvinyl ketone (IV), α,β-diphenylvinyl mesityl ketone (V), and α,β-diphenylvinyl duryl ketone (VI).


$\mathrm{Mes}\overset{\mathrm{CH_2}}{\overset{\|}{\mathrm{C}}}\mathrm{—CODur}$

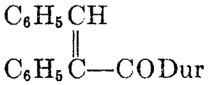
III


$\mathrm{Mes}\overset{\mathrm{CH_2}}{\overset{\|}{\mathrm{C}}}\mathrm{—CO—Idur}$

IV


$\mathrm{C_6H_5}\overset{\mathrm{C_6H_5CH}}{\overset{\|}{\mathrm{C}}}\mathrm{—COMes}$

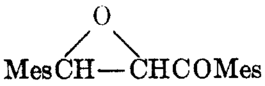
V

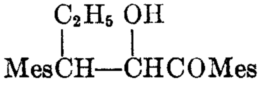

$\mathrm{C_6H_5}\overset{\mathrm{C_6H_5CH}}{\overset{\|}{\mathrm{C}}}\mathrm{—CODur}$

VI

The conversion of oxido ketones of this type to the corresponding unsaturated ketones appears to be general for Grignard reagents. With oxido mesityl α-mesitylvinyl ketone (II), ethylmagnesium bromide and phenylmagnesium bromide were used successfully. Ethylmagnesium bromide was used also with the oxides of ketones V and VI.

The reaction of ethylmagnesium bromide with the oxide of mesitalacetomesitylene (VII) was, however, one of normal addition. Although the structure of the addition product was not established, that shown in formula VIII seems probable.


VII


$\mathrm{Mes}\overset{\mathrm{C_2H_5}}{\overset{|}{\mathrm{C}}}\mathrm{H—}\overset{\mathrm{OH}}{\overset{|}{\mathrm{C}}}\mathrm{HCOMes}$

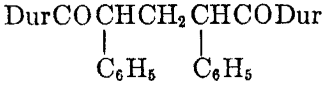
VIII

It is interesting that hydrogen iodide, the reagent normally used to convert oxido ketones to the corresponding unsaturated ketones (7), failed to remove oxygen from the oxide of mesityl α-mesitylvinyl ketone (II). The oxido ketone was isomerized by this reagent.

The α,β-Unsaturated Ketones

Of the eight unsaturated ketones which were used in this work, four were prepared by the condensation of the appropriate desoxybenzoins with formaldehyde. The method was that of Fuson and Sperati (8) who prepared three of them, namely, duryl α-mesitylvinyl ketone (III), isoduryl α-mesitylvinyl ketone (IV) and α-mesitylvinyl 2,4,6-triethylphenyl ketone. The fourth ketone of this group, mesityl α-mesitylvinyl ketone (I), was prepared by Fuson, Corse, and McKeever (9).

An attempt to use this method with benzyl duryl ketone produced a saturated substance which was identified as the bimolecular product, 1,5-diduryl-2,4-diphenyl-1,5-pentanedione (IX). Similarly, benzyl mesityl ketone yielded

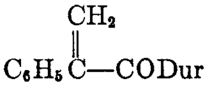

$\mathrm{DurCO}\underset{\mathrm{C_6H_5}}{\underset{|}{\mathrm{C}}}\mathrm{HCH_2}\underset{\mathrm{C_6H_5}}{\underset{|}{\mathrm{C}}}\mathrm{HCODur}$

IX

1,5-dimesityl-2,4-diphenyl-1,5-pentanedione.

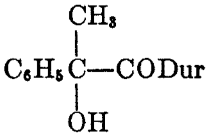
The remaining four α,β-unsaturated ketones were made by the condensation of the appropriate desoxybenzoins with benzaldehyde or *p*-chlorobenzaldehyde by the method of Fuson and Foster (10).

An attempt was made to prepare duryl α-phenylvinyl ketone (X) by condensation of duryl phenyl diketone with methylmagnesium iodide and dehydration of the resulting carbinol (XI). However, the dehydration could not be



$$C_6H_5\overset{\overset{CH_2}{\|}}{C}-CODur$$

X



$$C_6H_5\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}-CODur$$

XI

accomplished. Heating with 50% sulfuric acid had no effect. Acid of higher concentration changed the carbinol (XI) to an intractable oil. Similar results were obtained in attempts to make mesityl α-phenylvinyl ketone and α-phenylvinyl 2,4,6-triisopropylphenyl ketone from the corresponding diketones by this method. The difficulty of dehydrating keto alcohols of this type has been noted by Fuson and Robertson (11) and by Locquin and Heilmann (12), who employed fuming sulfuric acid to dehydrate carbinols of the type $R_2C(OH)COCH_3$.

EXPERIMENTAL[2]

THE α-OXIDO KETONES

The α,β-unsaturated ketones were converted to the corresponding oxido ketones by the method of Weitz and Scheffer (13). The unsaturated ketone was dissolved in methanol or ethanol and the resulting solution treated with an excess of alkaline hydrogen peroxide at room temperature. After the mixture had stood for a day or so, the alcohol was removed by distillation. When the residual solution was cooled, the oxide separated in a comparatively high state of purity. The melting points, crystallizing solvents, yields, and analytical data for these compounds are recorded in the Table. It will be noted that the yields were uniformly high, showing that the oxidation was unaffected by the crowding which characterizes the unsaturated ketones.

Reduction of the oxido ketones by Grignard reagents. The method used in the reduction of the oxido ketones consisted in adding the oxido ketone to a solution containing an excess of Grignard reagent. The reaction mixture was heated under reflux for three hours. The following procedure, used with oxido mesityl α-mesitylvinyl ketone, will serve to illustrate the method.

Reaction of oxido mesityl α-mesitylvinyl ketone with methylmagnesium iodide. Two and six-tenths milliliters of methyl iodide was added slowly to a mixture of 0.8 g. of magnesium and 50 ml. of dry ether. After the reaction had gone to completion (forty minutes), 1 g. of oxido mesityl α-mesitylvinyl ketone in dry ether was added slowly and the mixture heated under reflux for three hours. The reaction mixture was decomposed by pouring into a mixture of ice and hydrochloric acid, the ether layer was separated, and the water layer extracted with ether. The combined extracts were washed with sodium bicarbonate solution and water, and the ether was dried over magnesium sulfate. After filtration, removal of the ether by distillation left a white solid. This, when treated with Norit and recrystallized from ethanol, gave white crystals (m.p. 131–132°) which showed no depression in melting point when mixed with a known sample of mesityl α-mesitylvinyl ketone. The yield was practically quantitative when this reaction was carried out on a large scale.

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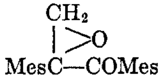
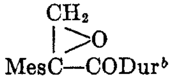
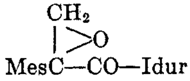
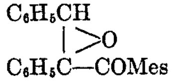
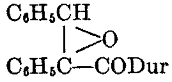
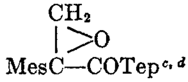
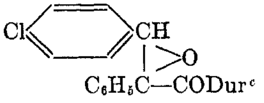
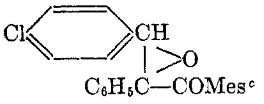
[2] Microanalyses by Miss Mary S. Kreger, Miss Margaret McCarthy, Miss Dorothy Schneider, and Miss Theta Spoor.

Substantially the same results were obtained with ethylmagnesium bromide and with phenylmagnesium bromide. The binary mixture, Mg–MgI_2, however, failed to effect reduction.

TABLE

α-Oxido Ketones

OXIDO KETONE	M.P.[a] °C	YIELD (%)	MOLECULAR FORMULA	ANALYSIS			
				Calc'd		Found	
				C	H	C	H
 $\begin{array}{l}\mathrm{CH_2}\\ \mid\!>\!\mathrm{O}\\ \mathrm{MesC{-}COMes}\end{array}$	152–152.5	95	$C_{21}H_{24}O_2$	81.78	7.84	81.93	7.92
 $\begin{array}{l}\mathrm{CH_2}\\ \mid\!>\!\mathrm{O}\\ \mathrm{MesC{-}CODur}^{b}\end{array}$	173–174	92	$C_{22}H_{26}O_2$	81.95	8.13	82.39	8.34
 $\begin{array}{l}\mathrm{CH_2}\\ \mid\!>\!\mathrm{O}\\ \mathrm{MesC{-}CO{-}Idur}\end{array}$	140.5–141.5	80	$C_{22}H_{26}O_2$	81.95	8.13	82.30	8.18
 $\begin{array}{l}\mathrm{C_6H_5CH}\\ \mid\!>\!\mathrm{O}\\ \mathrm{C_6H_5C{-}COMes}\end{array}$	88.5–89.5	95	$C_{24}H_{22}O_2$	84.18	6.48	84.06	6.82
 $\begin{array}{l}\mathrm{C_6H_5CH}\\ \mid\!>\!\mathrm{O}\\ \mathrm{C_6H_5C{-}CODur}\end{array}$	152–153	93	$C_{25}H_{24}O_2$	84.23	6.79	84.60	7.01
 $\begin{array}{l}\mathrm{CH_2}\\ \mid\!>\!\mathrm{O}\\ \mathrm{MesC{-}COTep}^{c,d}\end{array}$	99–99.5	85	$C_{24}H_{30}O_2$	82.23	8.63	81.87	8.82
	167–168	95	$C_{25}H_{23}ClO_2$	76.81	5.93	76.30	6.13
	131–132	95	$C_{24}H_{21}ClO_2$	76.48	5.62	76.08	5.63

[a] All melting points are corrected.

[b] This compound was recrystallized from methanol, the others from ethanol.

[c] This oxido ketone was not used in the Grignard study.

[d] Tep is used to designate the 2,4,6-triethylphenyl radical.

Reaction of oxido mesityl α-mesitylvinyl ketone with hydrogen iodide. A mixture of 10 g. of the oxido ketone, 300 ml. of glacial acetic acid, and 16 ml. of 50% hydriodic acid (sp. gr. 1.50) was heated under reflux for twenty hours. There was an immediate darkening of the mixture, which eventually became nearly black. It was cooled and poured into a mixture of ice and hydrochloric acid. The product, isomeric with the oxide, crystallized from chloroform in fine white needles which, when dried, assumed a chalky appearance; m.p. 250–253°.

Anal. Calc'd for $C_{21}H_{24}O_2$: C, 81.77; H, 7.85.
Found: C, 81.69; H, 7.91.

1,5-Diduryl-2,4-diphenyl-1,5-pentanedione (*IV*). A mixture of 5 g. of benzyl duryl ketone (10), 2 g. of paraformaldehyde, 150 ml. of ethanol, and 0.8 g. of potassium carbonate was warmed, with stirring, until the solids had dissolved. Twenty-five milliliters of water was added and the reaction mixture heated at 60°, with stirring, for eighteen hours. One gram each of paraformaldehyde and potassium carbonate was then added, and the heating and stirring were continued for an additional thirty hours. The orange-colored solution was poured into water which had been acidified with hydrochloric acid. The yield of crude 1,5-diduryl-2,4-diphenyl-1,5-pentanedione was 3 g. It was purified by repeated crystallization from aqueous acetone; m.p. 224–226°.

Anal. Calc'd for $C_{37}H_{40}O_2$: C, 86.00; H, 7.80.
Found: C, 85.89; H, 8.11.

Tests with permanganate and with hydrogen in the presence of a platinum catalyst showed the diketone to be saturated.

1,5-Dimesityl-2,4-diphenyl-1,5-pentadione.[3] A mixture of 5 g. of sodium hydroxide, 50 ml. of methanol, 23.8 g. of benzyl mesityl ketone, and 25 g. of 40% formalin was stirred at room temperature for forty-seven hours. It was allowed to stand for an additional thirty hours and poured into dilute hydrochloric acid. The diketone was extracted with ether and purified by recrystallization from ethanol; m.p. 206–207°.

Anal. Calc'd for $C_{35}H_{36}O_2$: C, 86.06; H, 7.38.
Found: C, 85.97; H, 7.82.

Duryl phenyl diketone. A mixture of 22.5 g. of selenium dioxide, 200 ml. of dioxane, and 8 ml. of water was heated and agitated until the solid had dissolved. To the solution was added 50.4 g. of benzyl duryl ketone (10) and then the mixture was heated under reflux for sixteen hours. The precipitated selenium was removed by filtration and the solvent by evaporation with an air blast. The dark, orange-colored diketone was recrystallized from methanol and from aqueous acetic acid; m.p. 76–77° (cor.).

Anal. Calc'd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81.
Found: C, 80.91; H, 7.07.

Methylphenyl-2,3,5,6-tetramethylbenzoylcarbinol (*XI*). A solution of 13.3 g. of duryl phenyl diketone in 70 ml. of dry ether was added, with stirring, to a solution of a Grignard reagent prepared from 2.4 g. of magnesium, 14.2 g. of methyl iodide, and 25 ml. of dry ether. The reaction mixture was heated under reflux for three hours and decomposed in the usual way. The carbinol was purified by recrystallization from aqueous acetic acid; m.p. 98–99° (cor.).

Anal. Calc'd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.86.
Found: C, 80.98; H, 7.94.

One-half gram of the carbinol was heated on a steam-bath for eight hours with 100 ml. of 50% sulfuric acid. It was recovered unchanged. When 65% sulfuric acid was used the carbinol was changed to a viscous amber oil from which no pure compound could be isolated.

Mesitoylmethylphenylcarbinol. This carbinol was prepared from mesityl phenyl diketone by the above method. It was an oil, boiling at 184–190° (5 mm.); n_D^{20} 1.5700.

Anal. Calc'd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51.
Found: C, 80.43; H, 7.66.

Methylphenyl-2,4,6-triisopropylbenzoylcarbinol.[4] This carbinol was prepared from phenyl 2,4,6-triisopropylphenyl diketone and methylmagnesium iodide. An attempt was made to synthesize the diketone by way of the corresponding benzoin by the method of

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[3] This compound was made by Dr. Norman Rabjohn.

[4] This compound was made by Dr. Quentin F. Soper.

Gray and Fuson (14). However, the condensation of 2,4,6-triisopropylphenylglyoxal with phenylmagnesium bromide gave only a small yield of the benzil. The benzil was obtained in 85% yields by the oxidation of benzyl 2,4,6-triisopropylphenyl ketone with selenium dioxide (15). The condensation of the benzil with methylmagnesium iodide afforded a 74% yield of the crude carbinol (m.p. 89–96°). The carbinol separated from dilute ethanol in slightly yellow crystals; m.p. 98–100°.

Anal. Calc'd for $C_{24}H_{32}O_2$: C, 81.77; H, 9.15.
Found: C, 81.73; H, 9.23.

Efforts to dehydrate the carbinol were unsuccessful.

Hydriodic acid reduction test. Enough oxido mesityl α-mesitylvinyl ketone to cover the tip of a small spatula was mixed with an equal amount of potassium iodide, added to 5 ml. of glacial acetic acid in a test tube, and heated gently. No color change was noted (A positive test is the appearance of a brown color due to the formation of free iodine.)

Reaction of oxido mesitalacetomesitylene with ethylmagnesium bromide. Thirteen milliliters of ethyl bromide was allowed to react with 4 g. of magnesium in 75 ml. of dry ether for one hour. Five grams of oxido mesitalacetomesitylene in 200 ml. of dry ether was added slowly and the reaction mixture was stirred and heated under reflux overnight. No gas was evolved during the reaction. The reaction mixture was decomposed with ice and hydrochloric acid, the ether layer was removed, the water layer was extracted with ether, and the extracts were combined. The resulting solution was washed with 5% sodium carbonate solution and with water and was dried over magnesium sulfate. When the ether was removed by distillation, there remained a white solid which was insoluble in boiling ethanol. It melted at 172–176°(cor.), resolidified at 176–180°(cor.), and melted again at 223–228°. Four recrystallizations from high-boiling petroleum ether gave fine, fluffy, white needles; m.p. 200–215°.

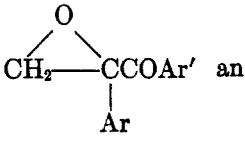
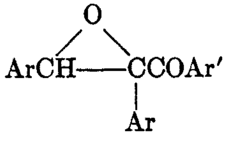
Anal. Calc'd for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93.
Found: C, 81.79; H, 8.85.

When 0.5 g. of the oxido mesitalacetomesitylene was allowed to stand in 95% ethanol with a trace of alkali for two months it changed to a yellow solid which had the melting point 131–142°. This compound was not studied further.

α,β-Diphenylvinyl mesityl ketone. A mixture of 10 g. of benzaldehyde, 10 g. of benzyl mesityl ketone, 100 ml. of ethanol, and 30 ml. of 10% aqueous sodium hydroxide solution was stirred at room temperature. After about fifteen minutes the solution became cloudy and an oil separated. Stirring was continued for three hours during which time the oil solidified. It was purified by recrystallization from ethanol; m.p. 82.5–83°; yield 11.2 g.

Anal. Calc'd for $C_{24}H_{22}O$: C, 88.29; H, 6.81.
Found: C, 88.37; H, 6.87.

SUMMARY

α-Oxido ketones of the types  $\overset{O}{CH_2{-}{-}\underset{Ar}{C}COAr'}$ and  $\overset{O}{ArCH{-}{-}\underset{Ar}{C}COAr'}$, in which Ar′ is a mesityl, duryl, or isoduryl radical, have been found to undergo loss of oxygen in the presence of Grignard reagents, the product being the corresponding α,β-unsaturated ketones.

The reaction, which is new in type, appears to be independent of the nature of the Grignard reagent used.

URBANA, ILL.

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(10) Fuson and Foster, *J. Am. Chem. Soc.*, **65**, 913 (1943).

(11) Fuson and Robertson, *J. Org. Chem.*, **7**, 466 (1942).

(12) Locquin and Heilmann, *Bull. soc. chim.*, **45**, 1107 (1929).

(13) Weitz and Scheffer, *Ber.*, **54**, 2327 (1921).

(14) Gray and Fuson, *J. Am. Chem. Soc.*, **56**, 739 (1934).

(15) Fuson and Soper, *J. Am. Chem. Soc.*, **65**, 915 (1943).